ADDITIONAL FEE:

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R E M A R K S

Submitted herewith is a new Power of Attorney for this application.

The Office Action issued February 16, 2007, has been received and its contents have been carefully noted.

The applicant, Kishore R. Shah, Ph.D., wishes to thank the Examiner in charge of this application, James. W. Rogers, Ph.D., for the courtesy and cooperation he extended during the telephone interview kindly granted on May 8, 2007. Prior to this interview, the applicant submitted a proposed Amendment for informal review by the Examiner. The Examiner acknowledged that applicant's proposed response to the aforementioned Office Action was "in the right direction", but requested that the applicant submit a supporting Declaration, verifying that the compositions disclosed in the applicant's prior U.S. patent No. 5,942,243 were not "homogeneous dispersions".

The Examiner also requested that the applicant file a Request for Continuing Examination or "RCE" because the independent claims were being amended after final Action.

The Declaration and the RCE are submitted herewith, together with a Power of Attorney to the undersigned counel.

The independent claims of this application -- namely, claims 1, 11, 16 and 17 -- have been amended to recite that the composition formed (claims 1 and 11) and used (claims 16 and 17) in the present invention is a "homogeneous dispersion" of its components. This amendment is supported by the specification, page 8, lines 19-32, especially lines 23-28, which state:

> "the Copolymer may be incorporated in the water phase by dispersing it under mechanical forces such as those produced by a homogenizer. A gel is a particularly appealing dosage form of the graft Copolymer of this invention. It was unexpectedly found that although the graft Copolymer is insoluble in water, it forms a very homogeneous and stable gel under high energy mixing as produced by a homogenizer."

Claim 11, as originally filed, also recites "a stable gel comprising the homogenized formulation of ... in an aqueous formulation... ".

The rejections of all the claims of this application as being anticipated over the U.S. Patent No. 6,106,820 to Morrissey or obvious over the combination of Morrissey and

the U.S. Patent No. 5,942,243 to Shah (the applicant herein) are respectfully traversed.

Before discussing this prior art - particularly the patent to Morrissey - it may be useful to review in detail the subject matter and background of the present invention.

Film-forming polymers constitute the most common class of materials suitable for delivery of biologically active materials to the human skin. Formulations, e.g. cream, lotion, or gel, containing the polymer delivery systems, when applied on the skin, quickly dry to form a polymeric film containing the non-volatile ingredients including the active molecules. Such a film can serve as a reservoir and a diffusion matrix for release of the actives to the skin. Although it would appear to be obvious to use polymeric materials as delivery system, there are significant challenges facing their application to skin. Skin being a living substrate, i.e. it breathes, perspires, stretches and contracts, the film formed must accommodate the various functions of the skin during different body activities and environmental conditions such as temperature and humidity. These are formidable challenges that may be encountered in skin product applications. In order to be compliant to these challenges, the polymeric film needs to be bioadherent

and have the viscoelastic properties, breathability, and moisture vapor permeability properties that are similar to skin. In the absence of such compliance, the film tends to feel uncomfortable or tight, peels, and flakes during use. The net result is inadequate wear time and loss of efficacy. Retention of the formed polymeric film on skin for the desired duration of time is a common problem that is encountered.

The present invention concerns a polymeric delivery system that is designed to address these issues.

The polymers used in this delivery system belong to a class of hydrophilic-hydrophobic graft copolymers having a combination of bioadhesive and controlled release properties. The graft copolymer based compositions for mucosal and skin applications were first disclosed in the U.S. Patent No. 5,942,243 to Shah. Formulations of the graft copolymer are useful for delivery of actives topically to skin as well as mucosal tissues, e. g. ocular, oral, rectal, nasal, and vaginal. The focus of the present invention is the use of these polymers for skin applications.

The graft copolymer used in the present invention has a hydrophilic polymeric main chain and a hydrophobic polymeric

side chain (see Figure 1, below). The main chain is comprised of monomeric units having acidic groups and neutral monomeric units. The preferred hydrophobic side chain moiety is polystyrene.

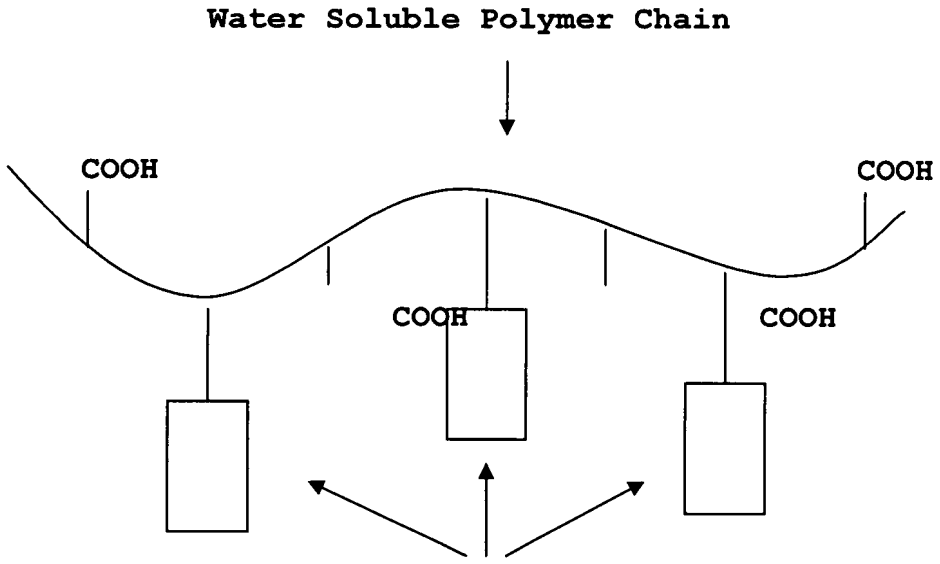

Figure 1: Schematic representation of graft polymer.

The monomeric moieties of the graft copolymer are selected to perform the needed functions. The acidic and neutral hydrophilic monomeric units provide the hydrophilicity to absorb aqueous fluids, whereas the polystyrene graft chains contribute to the integrity and water insolubility of the copolymer, thus resulting in a water swollen but insoluble jelly like mass in an aqueous environment. The acidic functionality of the copolymer in addition contributes to adhesion to the mucosal and skin

surfaces to maximize retention of the composition at the site of application. Release of the bioactive agent from the swollen polymer matrix occurs gradually by a process of diffusion. The hydrophilic neutral comonomer contributes to modification of the hydrophilicity and polarity of the graft copolymer for optimizing solubility of the active agents in it. The relative proportions of the three types of monomers determine the properties of the copolymer.

The graft copolymer exhibits microphase separation with a hydrophilic/hydrophobic domain system. The morphology of the graft copolymer is characterized by a hydrophilic continuous phase and a hydrophobic dispersed phase, which prevents the continuous phase from dissolving in water.

Claims 1 - 8, 10, 11 and 16 - 18 stand rejected as being anticipated by Morrissey. This rejection is respectfully traversed for the reasons given below.

Applicant's independent claims 1, 11, 16 and 17 each recite a composition comprising:

"(a) from about 0.3% to about 10% by weight of the total composition, of a graft Copolymer, comprising a hydrophilic polymer main chain comprising monomeric units, some of which have acidic groups, and a hydrophobic polymeric side chain comprising polystyrene..."

The patent to Morrissey unambiguously defines the side chains being <u>hydrophilic</u>. See, for example:

Abstract - Cover page.

"Disclosed are cosmetic compositions comprising: (a) from about 0.1% to about 50%, based on the weight of the composition, of a film-forming graft copolymer, wherein the copolymer comprises: (i) a backbone exhibiting a T.sub.g of from about 0.degree. C. to about 50.degree. C.; and (ii) one or more hydrophilic grafts attached to the backbone…".

Summary of the Invention - Column 1

"The present invention relates to cosmetic compositions having improved wear, preferably comprising:

(a) from about 0.1% to about 50%, based on the weight of the composition, of a film-forming graft copolymer, wherein the copolymer comprises:
(i) a backbone exhibiting a T.sub.g of from about 0.degree. C. to about 50.degree. C.; and

(ii) one or more hydrophilic grafts attached to the backbone wherein each of the grafts exhibits a T.sub.g of from about 50.degree. C. to about 200.degree. C., and …"

Column 3, lines 50-56

"The graft copolymers of the present invention exhibit one or more glass transition temperatures (T.sub.g). Preferred copolymers have at least two distinct immiscible phases, wherein the essential, hydrophilic polymeric side chains are closely associated with each other and exist in one phase and the polymeric backbone of the copolymer remains in a second separate phase. As a consequence of this phase immiscibility, the copolymer may exhibit at least two distinct Tg values, namely one T.sub.g value for the backbone and one T.sub.g value for the side chains, if the temperature separation between each of the T.sub.g values involved is large enough."

Column 5, section (b)

"b) Hydrophilic Grafts (Side Chains) of the Graft Copolymer
The copolymers of the present invention comprise from about 2% to about 50%, preferably from about 5% to about 40%, and more preferably from about 10% to about 30%, by weight of the graft copolymer, of hydrophilic side chains. Typically, the weight average molecular weight of the side chains is from about 1000 to about 50,000. The exhibit a T.sub.g of from about 50.degree. C. to about hydrophilic side chains 200.degree. C., preferably from about 60.degree. C. to about 150.degree. C., and most preferably from about 70.degree. C. to about 110.degree. C."

In contrast, the hydrophobic polystyrene graft side chains are essential and critical to the compositions of the present invention for the required properties, e.g. water insolubility and cohesive strength. The combination of the specified hydrophilic main chain and hydrophobic graft chains result in the desired properties (hydrogel formation,

water insolubility, cohesive strength and bioadhesion to skin) of the graft copolymers.

The Examiner has overlooked the fact that inclusion of small proportions of a hydrophobic monomer, such as styrene, do not make a polymeric graft hydrophobic. The essential comonomers for the hydrophilic graft chains are hydrophilic and are so described in the patent. It is well recognized in the field of polymer chemistry that one could use dimethylacrylamide, acrylic acid, and styrene to produce a hydrophilic graft chains. The use of styrene in some proportions does not make it hydrophobic. Hydrophilicity or hydrophobicity of a random copolymer is reflected by the totality of contributions of all monomers. Morrissey has defined the graft side chains as hydrophilic as formed by polymerizing a range of hydrophilic monomer(s) or its mixture with hydrophobic monomer(s). Morrissey does not describe the side chain polymeric graft as being hydrophobic anywhere in the specification.

Indeed, Morrissey has described the hydrophilic grafted side chains as being "essential" (see above in column 3) to produce a copolymer having the required properties of the compositions of his invention.

The Examiner's statement that Morrissey discloses a hydrophilic backbone in the claimed graft copolymers is not validated by the Morrissey patent specification. Just as in the case of the grafted side chains, copolymerizing some hydrophilic monomers with hydrophobic monomers does not necessarily make a hydrophilic copolymer.

Although the specification of the Morrissey patent does not so specify, it would be apparent to those skilled in the art that the backbone polymer would have to be hydrophobic to be able to retain the hardness, rigidity and toughness required for longer durability under the normal environmental use conditions described therein. It is well recognized by those skilled in the art that a graft copolymer with a hydrophilic backbone and hydrophilic side chains would not be expected to produce the wear and environmental stress resistant compositions disclosed by Morrissey. In fact, all the exemplary graft copolymers described in columns 7 and 8 have hydrophobic backbones.

The backbone or main chains of the present invention are hydrophilic by definition (neutral and acidic hydrophilic monomeric units). These graft copolymers form hydrogels in an aqueous environment. No such hydrogel formation is disclosed by Morrissey.

In summary, the graft copolymers of Morrissey and the present invention are both structurally and chemically very different entities.

Claims 1-4, 6-8, 10-11 and 16-17 stand rejected as being unpatentable over the U.S. Patent No. 5,942,243 to Shah. Claims 1-8, 10-11 and 16-18 also stand rejected as being unpatentable over Shah in view of Morrissey. These rejections are also respectfully traversed, for the reasons given below.

The compositions of the present invention differ significantly from those of Shah. The compositions of the present invention incorporate the polymeric ingredients described in Shah with acceptable dermatological carriers to form compositions capable of *in situ* forming a film on skin and which film exhibits strong bioadhesion to provide a long lasting treatment on skin.

A full discussion of the differences over Shah may be found on pages 5 and 6 of Applicant's Amendment filed November 30, 2006.

In particular, applicant's independent claims 1, 11, 16 and 17, each recite a composition comprises "a homogeneous dispersion" of components (a), (b) and (c).

The resulting composition not only differs from the composition of Shah but also produces surprising effectiveness as a dermatological delivery system.

Both the film formation from the claimed composition and bioadhesion to skin of the formed film are unanticipated and non-obvious. Although the compositions of Shah form a water-insoluble hydrogel in water, it was unexpectedly discovered that upon homogenization, as in a laboratory blender or by means of a Silverson-type homogenizer, the hydrogel forms a very stable dispersion which is almost "solution like" and has a slight bluish haze. When the dispersion dries on a skin surface, it forms a water-insoluble bioadherent film.

The aqueous dispersion of the polymer also has a tendency to generate foam under mechanical agitation which takes several hours to subside. This behavior seemed to indicate that the polymer with its duel hydrophobic and hydrophilic characteristics could be functioning as a polymeric emulsifier to stabilize the foam. Another indication of its emulsifier function was observed in the formation of very stable milk-like emulsions of water-soluble compounds when mixed in an aqueous dispersion of the polymer. Thus, aqueous dispersions of the Shah polymer

provide a useful means for solubilization of water-insoluble drugs and other dermatological and cosmetic additives

Without the formation of such micellar-like aqueous polymer solutions in water, the graft copolymers would have had very limited or no utility in the dermatological product applications. In fact, it was the discovery of formation of such solutions (instead of lumpy gel fragments as would have been expected from a hydrogel forming graft copolymer) that led to the compositions of the present invention. It may be noted that while the formation of such solutions in water may be a new property or function, development of dermatological formulations using this property is an invention.

Submitted herewith, at the request of the Examiner, is a Declaration of the applicant/inventor stating affirmatively that the compositions disclosed in applicant's own prior U.S. patent ('243 patent) were not homogeneous as is now positively recited in each of the independent claims 1, 11, 16 and 17. This Declaration also points out that Morrissey's side chains which are hydrophilic, as compared to applicant's side chains which are hydrophobic, result in significantly different physical properties than applicant's claimed composition.

In conclusion, neither Morrissey nor Shah anticipate the claimed composition, nor do they teach, suggest or provide motivation to produce the claimed composition for use as a bioadherent polymeric film for the skin.

This application is therefore believed to be in condition for immediate allowance. A formal Notice of Allowance is accordingly solicited.

Respectfully submitted,

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